

PRESERVATION OF OVARIAN GERMINAL FOLLICLES BY TEMPORARY LAPAROSCOPIC OVARIAN TRANSPOSITION IN TEENAGED GIRLS UNDERGOING CRANIOSPINAL IRRADIATION FOR RADIOSENSITIVE CENTRAL NERVOUS SYSTEM TUMORS

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SUMMARY

Objective: To report the efficacy of laparoscopic ovarian transposition procedure in teenaged girls for preventing ovarian damage from craniospinal radiation therapy.

Materials and Methods: Five teenaged girls were diagnosed with radiosensitive brain germinomas or medulloblastomas that needed irradiation with doses of higher than 500 cGy to the whole craniospinal area after craniotomy. The oophoropexy method was lateral transposition of the ovaries to the round ligament without opening the surrounding peritoneum so as to move the ovaries outside of the radiation field. Meanwhile, the hemoclip was clamped on the medial site of the ovary to guide the radiologist to set a proper field between the two ovaries for radiation therapy. After irradiation with the total dose completed, second-look laparoscopy was performed to remove the Prolene stitches and hemoclips. Bilateral ovarian biopsies were performed to evaluate the efficacy on the preservation of ovarian tissue, upon the consent of each patient and her parents.

Results: On second-look laparoscopy, only small amounts of loose adhesions surrounding the hemoclips and ties were found. Histologic measurements showed that there were more than 10 germinal follicles per high-power field in each ovarian tissue section.

Conclusion: Laparoscopic oophoropexy is an easy and safe surgical procedure for teenaged girls. It can be used to successfully prevent craniospinal irradiation damage to the ovarian germinal follicles in teenaged girls and to retain their ovarian reproductive function. [*Taiwan J Obstet Gynecol* 2008;47(3):300–304]

Key Words: germinal follicle, germinoma, laparoscopy oophoropexy, medulloblastoma, ovarian transposition, radiotherapy

Introduction

Radiation therapy for the treatment of various human cancers, in which the field includes either the pelvis or the

whole craniospinal neuraxis, carries a high risk of irreversible damage to ovarian reproductive function. Dose-related gonadal castration has been reported after a total irradiation dose of higher than 500 cGy was delivered to the ovaries [1]. This severe iatrogenic complication should be minimized as much as possible. In addition, it is well recognized that with advances in cancer treatment modalities, the maintenance of the quality of life after survival is as necessary as the success of treatment, as well as the minimization of treatment-related morbidity and mortality. Preservation of ovarian



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function to avoid premature iatrogenic aging and to maintain fertility potential has become an important part of modern cancer management, and should be considered as the right of women of reproductive age [2].

A common way to determine whether the ovarian function is preserved after irradiation is to follow the menstrual patterns associated with sex hormone assessment. However, for pubertal teenaged girls with radiation-sensitive central nervous system malignancies receiving whole craniospinal irradiation, observation of the menstrual patterns alone may cause some misinterpretations, because the neuroendocrine portion of the hypothalamic-pituitary-ovarian axis is distorted, either anatomically or functionally. In addition, for the prepubertal girl whose menarche has not occurred yet, it is impractical to wait for menstruation initiation to determine the ovarian function. Thus, we suggest that second-look laparoscopy be performed to reposition the ovaries and confirm the preservation of ovarian germinal follicles after the completion of radiotherapy.

Materials and Methods

Subjects

Three prepubertal and two pubertal teenaged girls presented with severe headaches and nausea. Imaging studies with magnetic resonance imaging led to the diagnosis of hydrocephalus with increased intracranial pressure in these girls. Each girl underwent craniotomy with ventriculoperitoneal shunting procedures to relieve intracranial pressure and local excision and/or biopsy on the tumor. Histologic examination revealed germinoma or medulloblastoma in tissue samples (Table). Irradiation treatment plan was scheduled to treat the radiosensitive tumors for 1–2 months, in which the field included the whole craniospinal axis down to the sacral level. Prior to the commencement of radiotherapy, a gynecologist was consulted for laparoscopic transposition of the ovaries, so that irradiation-induced gonadal damage could be minimized and the childbearing potential would be preserved. Informed consent was obtained for the procedures from the parents. The characteristics of the patients are shown in the Table.

Laparoscopic procedure

The laparoscopic procedure comprising three puncture trocars with one 10-mm infraumbilical and two 5-mm suprapubic ports under general anesthesia was performed as described previously [3]. After creating the pneumoperitoneum, a 1-0 polypropylene monofilament nonabsorbable suture (Ethicon; Johnson-Johnson, NJ, USA) was passed using a ski needle swaged from a

Table. Patient characteristics

Case	Age (yr)	BMI	Age at menarche (yr)	Tumor		Laparoscopic surgery time course* (hr)	Radiation dose (cGy)/no. of fractions			Outcome of follow-up	
				Location	Pathology		Whole brain	Boost to tumor	Spinal area [†]	Ovarian biopsy primordial follicle	Years of NED/years after surgery
1	16	16.7	NA	Third ventricle	Germinoma	1	2,520/14	5,040/28	2,380/14	(+)	11/11
2	16	17.2	12	Pineal body	Germinoma	0.6	2,380/14	5,440/32	2,380/14	(+)	1/3 (DOD)
3	11	20.2	NA	Pineal body	Germinoma	0.6	2,340/14	5,040/28	2,340/14	(+)	8/8
4	17	18.4	13	Cerebrum	Medulloblastoma	0.6	3,600/20	5,580/31	3,600/20	(+)	3/3.5
5	12	16.5	NA	Cerebellum	Medulloblastoma	0.6	3,600/20	5,600/30	3,600/20	NA	1/2 (DOD)

*Laparoscopic surgery for lateral ovarian transposition and set the hemoclip; [†]from the first cervical spine level down to the sacrum. BMI = body mass index; NED = no evidence of disease; NA = not applicable; (+) = present; DOD = died of disease.

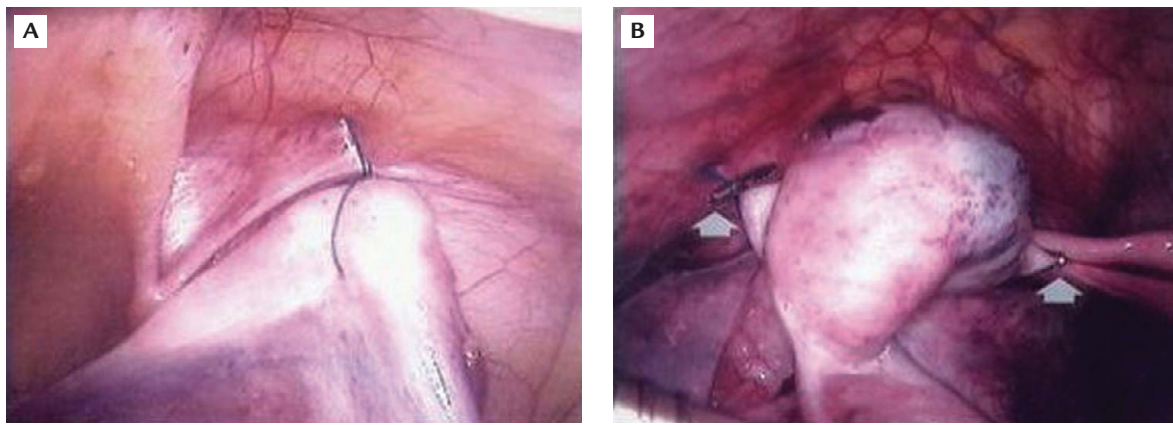


Figure 1. Laparoscopic ovarian transposition. The ovary is superolaterally displaced and anchored to the abdomen in: (A) Case 1 at prepuberty, right ovary, and (B) Case 2 at puberty, left ovary (the arrows indicate the metal hemoclips).

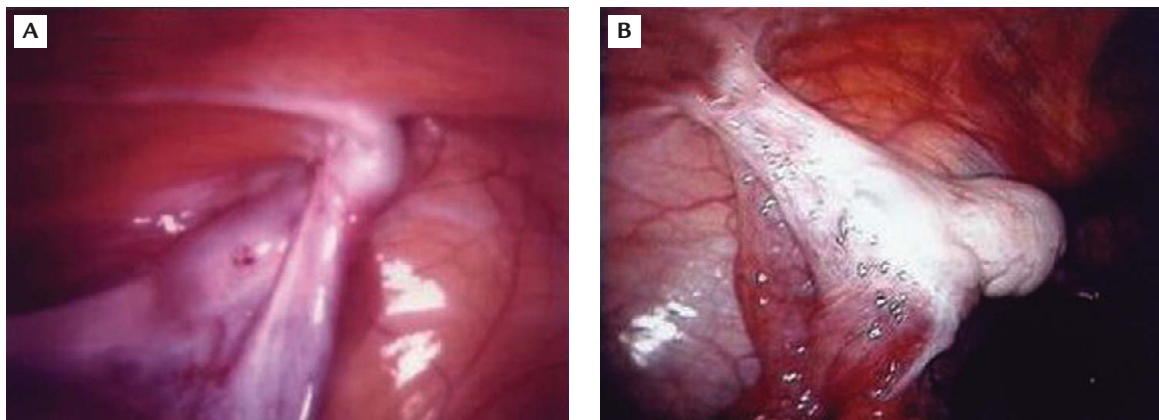


Figure 2. Local adhesion formation is found during second-look laparoscopy in: (A) Case 1, and (B) Case 2.

curved needle inwards through a 1-cm transverse skin incision inferomedial to the anterosuperior iliac spine. To suspend the ovaries, the ski needle held by the laparoscopic needle holder was used to make a single stitch through the middle of the prepubertal ovary (Figure 1A) in Case 1, and a figure-eight suture was used around the mature ovary in Case 2 (Figure 1B). In Case 2, the first stitch of the suture was placed through the caudal part of the ovary beneath the ovarian ligament mediolaterally and the second stitch through the middle of the ovarian body. After securing the ovary, the needle was drawn back out of the abdominal cavity through the fascia under the skin incision and kept 1.0 cm from the inbound suture site. During placement of the suture, the peritoneum was never opened, being punctured only by the needle and three laparoscopic ports, allowing the ovarian ligament to remain intact [4,5]. Two hemoclips (10 medium-large titanium; Weck Closure Systems, NC, USA) were used, with one clamped on the ovarian ligament and another placed and clamped on the Prolene stitch in the ovary (Figure 1B). The Prolene stitch was tightened

extracorporeally to raise and pull the ovary up to the peritoneum, which ensured that good transposition had been achieved with properly placed stitches. A knot was then made on the abdominal fascia. The same procedure was then performed for the contralateral ovary.

Both patients commenced radiotherapy 1 week after the surgery. The medial borders of the ovaries were identified by radiographic imaging of the hemoclips, which were lying away from the sciatic notch when the patients were in the prone position. The fields and doses of irradiation are given in the Table. A second-look laparoscopy was performed at 2 years and 6 months in Cases 1 and 2, respectively, after the course of irradiation was complete. The gross appearance of the ovaries had changed little, and local adhesion formation between the upper part of the ovary and the peritoneum was noted (Figure 2). Adhesiolysis and removal of the metal clips and Prolene sutures took place without difficulty. A 0.5 × 0.5 × 0.5 cm piece of cortical tissue from the anterior border of the ovary was taken to determine whether the germinal follicles were preserved.

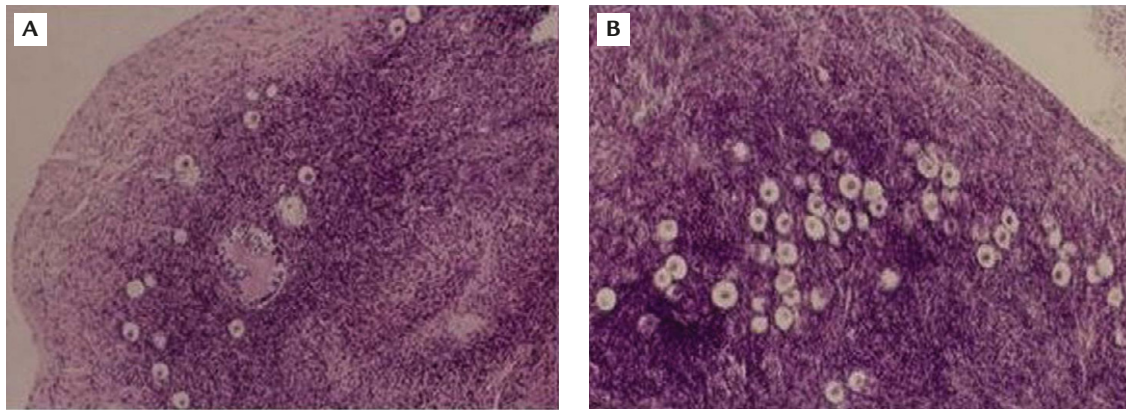


Figure 3. Germinal follicles are preserved on microscopic examination (hematoxylin and eosin stain, 100×) in: (A) Case 1, and (B) Case 2.

Results

All patients tolerated the procedures well and recovered rapidly after both laparoscopies. Mild tightness and pain were reported on the abdominal wound in which the ovary was anchored, but subsided weeks after the first laparoscopy. Histologic examination showed normal-growing ovarian germinal follicles (Figure 3). At the time of writing, no patient had shown evidence of disease for 11 years (Case 1), 8 years (Case 3), 3 years (Case 4) and 1 year (Cases 2 and 5). Unfortunately, Cases 2 and 5 died of tumor recurrence, and metastasis occurred to the bone and liver. The two prepubertal girls failed to initiate sexual characteristic development, and amenorrhea persisted owing to panhypopituitarism.

Discussion

A variety of neuroendocrine disturbances have been observed following treatment with craniospinal neuraxis radiation therapy for radiosensitive central nervous system malignancy [6]. The sequelae result from irradiation-induced ovarian germinal cell depletion and/or pituitary neuroendocrine cell damage. The severity is dose-dependent. In an attempt to preserve reproductive function, transposition of the ovaries outside of the irradiation field and adjustment of optimal radiation dose are critical in terms of the hypothalamic–pituitary–ovarian axis. In the past, assessment of post-irradiation ovarian function mainly depended on the determination of serum gonadotropin levels and return of menstruation. However, for prepubertal girls who are hypogonadotropic and have not experienced menarche, it is impractical to evaluate the ovarian function by our two cases. Furthermore, radiation-induced abnormalities may be transient or develop many years after the initial

treatment. So, even for girls after puberty, the return of menstruation may or may not be sufficient to assess the possible diminished ovarian reserve with loss of ovarian follicles. An approach of histopathologic examination of ovarian biopsies for the distribution of germinal follicle would be a promising method to evaluate the ovarian reserve. Vital et al used laparoscopic ovarian biopsies on patients with clinically diminished ovarian function and found that the number of primordial follicles strongly related to those with premature ovarian failure, low ovarian reserve, and the healthy control subjects [7].

In addition to moving the ovary outside of the irradiation field, avoidance of mechanical disruption on ovarian blood supply and surrounding ligaments during the transposition procedure is also important. Data from a study on patients with early stage cervical cancer undergoing surgical management showed that only 17% of patients who had ovarian transposition with the fallopian tube and utero-ovarian ligament cut and ligated prior to pelvic radiation had continued ovarian function [8]. It is certain that fewer injuries on the ovary *per se* and blood supply vessels allow for more subsequent ovarian reproductive functions.

In our experience, laparoscopic transposition without the need for excision of adnexal surrounding tissues was able to move the ovary outside of the irradiation field and protect the ovary from damage using local doses of 2,300–2,500 cGy along the lumbosacral axis. The procedure was simple and effective.

The second-look laparoscopy demonstrated that the ovary was preserved bilaterally, with only ovarian adherence to the peritoneum at the previous suture sites noted. Histologic demonstration of ovarian germinal follicles confirms that the ovaries were well saved. For long-term follow-up, evaluation of the hypothalamic–pituitary hormonal secretion is good in the assessment of hypothalamic–pituitary–ovarian function in reproduction.

The use of ovarian displacement prior to irradiation has been described previously in the context of various pelvic cancers, such as cervical cancer, vaginal cancer [1,2] and colorectal cancer [4,5], as well as lymphoma [1] and brain medulloblastoma [9]. The main factor contributing to successful preservation of ovarian function is adequate transposition. Different cancers need to be irradiated to different degrees and extents in the pelvis. For those who undergo craniospinal irradiation, as described in this report, lateral displacement of the ovaries without transection of the ovarian ligament and peritoneum can provide sufficient transposition to allow ovarian function to be preserved.

The laparoscopic approach, as opposed to conventional laparotomy, offers advantages including minimal wound incisions, reduced postoperative pain and hospital stays, as well as rapid recovery [3,5]. Additionally, the laparoscopic procedure requires only 40–60 minutes of theatre time to complete. We suggest that ovarian transposition could be performed concomitantly during ventriculoperitoneal shunting procedures without compromising postoperative recovery, when intraoperative diagnosis of frozen section tumor biopsies is possible.

The second-look laparoscopy provided a unique opportunity to demonstrate the adhesion sequelae of ovarian transposition, restoration of normal ovarian position, and confirmation of germinal follicle preservation that proved useful in the differential diagnosis of the post-irradiation menstrual disorders. Studies of patients with pelvic cancer showed that the prognosis for fertility was excellent (80% pregnancy rate) after ovarian transposition and irradiation, if the genital tract remains morphologically normal [2]. Although the prepubertal patients had not initiated puberty and experienced ovulatory disturbances with oligomenorrhea after radiotherapy, all of them retained the potential for fertility, since the ovarian germinal follicles, which responded to exogenous gonadotropin administration, were preserved.

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